The Epidemic of Chronic Kidney Disease in USA and in the World: Causes and Prevention

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May 10, 2021
Evolution and Survival

• Human being and environment are interrelated in a dynamic but fragile equilibrium.
• Humans have always struggled for survival facing environmental challenges, adversities, epidemics, and exposure to toxins.
• On the other hand, human beings have had a tremendous impact on the environment, magnified in recent times.
Hunter Gatherer to Agriculture

~10,000 years ago

Sheep, Cattle, Goats

Mesopotamia
The Development of Relationship between Human and Geography

• *The second stage (from 250 years ago)*
  • in the 18th century, the second revolutionary leaps occurs with the development of machineries to help in the production chain. It is the beginning of the industrial civilization).

• The 19th century, is marked by the development of internal combustion engine and the use of electricity.
The Development of Relationship between Human and Geography

- **The third stage**: With the 20th century, mankind started the third technological revolution.
  - Non-renewable fossil fuel energy (coal, oil, nuclear energy)
  - Electronic computers, and space technology

- From manual labor to machine production.

- From agriculture and animal husbandry to the commodity economy.

- This resulted in an unprecedented increase of productivity, and wealth, but also in new forms of environment pollution, such as plastic, space junk, nuclear radiation, noise pollution, automobile exhaust, light and electromagnetic pollution, and a more sedentary life-style.
The GREEN Revolution or Third Agricultural Revolution (1950-70)

• The key leader was Norman Borlaug (Nobel Peace Prize 1970)
• Introduction of chemical fertilizers and agro-chemicals (Pesticides, and herbicides)
• Improved irrigation and mechanization
• High yielding hybridized seeds for a varieties of cereals
• This initiative increased supply of grain, has led to cheaper livestock and is credited with saving over a billion people from starvation

• But, at what cost for the environment and the human species?
Agricultural Dust Exposure
Humans and the Environment

- Continuous and increasing rate of exploitation of natural resources, industrialization, technological growth, and unplanned urbanization are responsible for grave environmental crisis and ecological imbalance (Ex. Global Warming).
But Careful !!!

• Nature is vengeful against those that try to subvert it.

• Many animal species have been wiped out from earth. Even the powerful dinosaurs.

• **Humanoids are no exception. !**
What has been the Impact of these Revolutions on Public Health?
Three Major Consequences

1. Transformation from manual labor to machinery and computers $\rightarrow$ More sedentary life
2. Increased availability of cheap and abundant food $\rightarrow$ Increased food intake
3. Increased pollution of the environment $\rightarrow$ increased exposure to poisons
4. The use of new medicines and diagnostic agents have contributed to prolonging life, but have introduced a new array of poisons that adversely affect health
Obesity and Diabetes Trends in the US

Primary Diagnoses For Patients Who Are On Dialysis Or Start Dialysis

Prevalence:
- DM: 38%
- HTN: 26%
- Other: 16%
- Cystic: 7%
- GN: 2%

Incidence:
- DM: 47%
- HTN: 28%
- Other: 16%
- Cystic: 7%
- GN: 2%

USRDS 2016
Definition of CKD (NKF-DOQI)

- Condition that affects the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function such as CVD

<table>
<thead>
<tr>
<th>Working criteria. One of the following:</th>
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<tbody>
<tr>
<td>Kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney, manifest by either:</td>
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<tr>
<td>- Pathological abnormalities; or</td>
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<tr>
<td>- Markers of kidney damage (abnormalities in blood, urine, or imaging tests)</td>
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<td>GFR &lt; 60 mL/min/1.73m² for 3 months</td>
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www.kidney.org/professionals/KDOQI
# National Kidney Foundation: Stages of CKD*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Clinical Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
<td></td>
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<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>CKD</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>Advanced CKD</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>ESRD</td>
</tr>
</tbody>
</table>

*In patients >20 years of age

Are we using the right sensors to detect CKD?
Serum Cr is insensitive marker of reduced GFR

MDRD: cohort of 1628 pts aged 18-70 with chronic renal disease not on dialysis who underwent GFR measurement by $^{125}$I-iothalamate clearance

Levey 1999, Ann Int Med 130:461
Limitations of isolated, unstandardized serum Cr

- \( \text{GFR} = \frac{U_{\text{Cr}} \cdot V}{\overline{S}_{\text{Cr}}} \) Highly lab dependent
Fallacies of Serum Creatinine

*Three Patients with Creat = 1 mg/dL*

1. Patient weighs 50 Kg and produces 1 g of creatinine/24 h → GFR = 70 ml/min
2. Patient weighs 75 Kg and produces 2 g of creatinine → GFR = 140 ml/min
3. Shaquill O Neal 100 Kg and produces 3 g of creatinine → GFR = 210 ml/min
Limitations of isolated, unstandardized urine Cr

- \( \text{GFR} = \frac{\text{U}_{\text{Cr}} \cdot \text{V}}{\text{S}_{\text{Cr}}} \)
  
  = Cr generation rate

  Depends on age, gender, muscle mass, diet and Urine collection
24 hour urine Cr clearance to estimate GFR

- Inaccuracy linked to method used to measure creatinine
- Inaccurate urine collection
- Overestimates GFR due to tubular secretion of creat.
  - Can correct by averaging creat. and urea clearance
Direct measurement of GFR

- $^{125}$I-iothalamate
- Inulin clearance
- $^{99m}$Tc-DTPA radionuclide scan
Estimates of Renal Function

- **Cockcroft-Gault:**
  - CrCl: \[
    \frac{[(140 - \text{age}) \times \text{Weight (kg)}]}{\text{SCr} \times 72} \times 0.85 \text{ if female}
  \]

- **MDRD***:
  - GFR: \[(\text{SCr})^{0.203} \times (\text{Age})^{0.176} \times (0.742 \text{ if female}) \times (1.210 \text{ if AA})\]
  - Example:
    - 67 y.o. white male with serum creatinine 1.4 has estimated GFR of 55 by MDRD (Average GFR for age 60–69 yrs is 85)

Clinicians are often unaware of the degree of renal insufficiency by looking at SCr alone.

*MDRD formula recommended for use by the National Kidney Disease Education Program www.nkdep.nih.gov.
Microalbuminuria: Does it predict CKD?

- Microalbuminuria is considered a predictor of subsequent kidney disease.
- In Type 1 diabetes, microalbuminuria predicts progression in ~ 90%.
- In type II only 35-40% of pts with microalbuminuria develop overt proteinuria over 10 years.
- In non-diabetic patients the predictive value of microalbuminuria for progressive kidney disease is not well established.
Proteinuria is an independent risk factor for kidney disease, CVD and mortality.

\[ P<0.01,\text{ normo- vs micro- and macroalbuminuria.} \]
\[ P<0.05,\text{ micro- vs macroalbuminuria.} \]

Take home messages

- CKD is defined by GFR < 60 or other evidence of renal damage for ≥ 3 months
- GFR should be estimated from serum Cr by the MDRD equation but clinicians should be aware of overestimation when GFR is near or > 60 and in Asians
- The prevalence of CKD is uncertain, but it is probably 10-13% in the adult population
- Although microalbuminuria is associated with increased risk of CVD and CKD, it should not be used to define CKD
- CKD is associated with increased risk of death, CVD
- CKD is also a risk factor for progression to ESRD but 1/4 of patients do not progress and 90% die before reaching ESRD due to CV disease
The Kidneys are particularly Susceptible to Environmental Factors
Renal Blood Flow and its Regulation

• High blood flow: 1200 ml/min, 25% of cardiac output, 50x higher than to other organs
• A high blood flow is necessary for glomerular filtration
• Distribution
  – Cortex 90%
  – Outer medulla 9%
  – Inner medulla 1%

Vasa rect are 40 mm long
Low hidrostatic pressure
High viscosisty
Smog and Mortality

- WHO estimates that 92% of the world’s population lives in places where air quality levels exceed WHO limits.
- In Europe, it is estimated that exposure to excessive particulate matter > 2.5 m (PM$_{2.5}$) causes more than 400,000 premature deaths/year.
- In China, in 2010 excessive PM$_{2.5}$ caused more than 1.2 million premature deaths, 42% higher than the level in 2000.
Susceptibility of the kidney to environmental attacks

• Given their secretory and excretory functions, and hyperosmolarity in the medulla, the kidneys are commonly victimized by:
  – circulating antibody/antigen complexes
  – environmental toxins
  – Drugs ingested for therapeutic reasons (non-steroidal anti-inflammatory agents, antibiotics, lithium, platinum, immunosuppressive and anticancer agents), or recreational reasons (heroin, cocaine and amphetamines).
  – Diagnostic agents (such as contrast agents).
The association between urbanization and reduced renal function: the China Health and Nutrition Survey (BMC Nephrol. 2017; 18: 160.)

• The prevalence of reduced kidney function was 8.1% among 3644 men and 4154 women, aged 18 to 94 years

• Using a validated, multi-component urbanization index, a positive association was found between urbanization and reduced kidney function.
Prospective associations between environmental heavy metal exposure and renal outcomes in adults with CKD in Taiwan (doi: 10.1111/nep.13089)

• From January 01, 2003 to June 30, 2015, the authors retrospectively identified 2343 CKD patients with an eGFR of <60 mL/min/1.73 m² at one tertiary care center, in Taiwan.
• Patients were followed for 3.49 ± 2.27 years, until death or initiation of maintenance dialysis.
• There were high correlations among the concentrations of eight metals (arsenic, cadmium, chromium, mercury, copper, lead, nickel, and zinc) and the risk of ESRD.
A study, from St. Louis VA Medical Center, looked at 2.5 million veterans who did not have kidney disease when they were screened in 2003 and 2004. Their cases were “followed” across the country for an average of 8.5 years and compared to air pollution levels across the country being monitored by the Environmental Protection Agency (EPA) and the National Aeronautics and Space Administration (NASA). For accuracy, researchers also took into account other risk factors (age, race, sex, heart disease, lung disease, diabetes, high blood pressure, smoking, obesity, and poverty).
Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD

**METHODS**
- Observational cohort of 2,482,737 US Veterans followed for 8.92 years
- Fine particulate matter <2.5 μm in aerodynamic diameter (PM$_{2.5}$) exposure data
- EPA ground-based air monitoring stations
- NASA satellites spaceborne sensors

**OUTCOMES**
- Increase in Risk of Kidney Outcomes for Every 10 Increase in PM$_{2.5}$ (µg/m$^3$)
- National Burden of Incident CKD Attributable to PM$_{2.5}$ Exposure Above the EPA recommended level of 12 µg/m$^3$

**CONCLUSION**
- Our findings demonstrate a significant association between exposure to ambient PM$_{2.5}$ and risk of incident CKD, eGFR decline, and ESRD.

Benjamin Bowe et al. JASN 2018;29:218-230
Geographic distribution of the national burden of incident CKD attributable to air pollution in the United States.

Benjamin Bowe et al. JASN 2018;29:218-230
Balkan Nephropathy

• BN is an endemic chronic tubulointerstitial nephritis affecting residents of rural villages located in valleys near tributaries of the Danube River in Bosnia, Bulgaria, Croatia, Romania, and Serbia.

• Epidemiologic features:
  – focal occurrence in certain farming villages, with unaffected villages located in close proximity;
  – a familial but not inherited pattern of disease;
  – occurrence only in individuals older than 18 yr
  – strong association with upper urinary tract transitional cell (urothelial) cancer

JASN November 2007 vol. 18 no. 11 2817-2823
Balkan Nephropathy
ARISTOLOCHIC ACID AND ENDEMIC NEPHROPATHY

- Jelaković (Zagreb) drew attention to the fact that in Croatia nephrotoxicity was common in horses that ingested hay contaminated with *Aristolochia clematitis*, a plant containing aristolochic acid.

  - Since seeds of *A. clematidis* commingled with wheat grain during the annual harvest, a toxic constituent in this plant might be inadvertently introduced into home-baked bread.

- Remarkably, during the next 35 yr, no attempt was made to confirm or follow up on this hypothesis.
ARISTOLOCHIC ACID AND ENDEMIC NEPHROPATHY

• Grollman et al at Stony Brooks, NY, (Proc Natl Acad Sci U S A 104 : 12129 –12134, 2007) used ultrasensitive, quantitative 32P-postlabeling methods, in conjunction with HPLC and mass spectroscopic techniques, to quantify dA-aristolactam (dA-AL) and dG-aristolactam (dG-AL) adducts in the renal cortex of patients with endemic nephropathy and in urothelial cancer tissues of residents of endemic villages.

• In urothelial cancers cells removed at surgery from patients residing in the endemic region he demonstrated that A:T→T:A mutations were dominant in the p53 gene.
Aristolochia clematitis and Aristolochic Acid Formula
CHINESE HERBAL NEPHROPATHY =
ARISTOLOCHIC ACID NEPHROPATHY

• Aristolochia species have been used widely for more than 2000 years in Chinese medicine as well as in Europe, Latin America, and the United States.

• Herbal recipes used in Roman-Greco times contained Aristolochia in amounts estimated to be highly nephrotoxic.

• The potent toxicity of Aristolochia in humans was appreciated only in the early 1990s.

• Nortier (N Engl J Med 342: 1686–1692, 2000), described 112 patients with a diagnosis of Chinese herb nephropathy, with renal failure. Among the latter, removal of the native kidneys and ureters revealed a high prevalence (>40%) of urothelial cancer in the upper urinary tract, a highly unusual site for transitional cell cancers.

• Subsequently, additional cases of so-called Chinese herb nephropathy were reported worldwide.
Epidemiology of CKDu in the World

• In the last 2-3 decades there has been an unexplained increase in the incidence of CKD, in some regions of Central America, India, Africa and Asia.
• This epidemic does not appear to be linked to cardio-metabolic causes and is called **CKD of uncertain origin (CKDu)**
World Epidemic of CKDu
Epidemiology of ESRD in Central America

• The first formal mention of the possible presence of a new pathologic entity was published in 2002 by Trabanino et al. (Rev Panam Salud Publica 2002;12:202-206), who reported that 67% of patients with advanced CKD in El Salvador had a disease of unknown origin.

• Subsequently, several other investigators have reported a high incidence of CKD in various regions of Central American for which the cause(s) remain unknown.
Distribution of CKDu
Mesoamerican Nephropathy

- Occurs predominantly along the Pacific coast, much less in the hills (?)
- Affects primarily young men working in sugar cane fields, miners, construction workers, fishing industry, port workers, brick-makers.
- It may affect women and children
Sugar-Cane Harvesting
Meso-American Nephropathy Presenting as CKD

• A randomized (unpublished) survey of 10% of the general population in MalPaisillo (Leon, Nicaragua); 26,000 people
  – 27% of the screened participants manifested abnormal serum creatinine;
  – 35% had hyperuricemia.
• Urinalysis showed minimal proteinuria, some leukocytes

Bigazzi and Bianchi, unpublished data
Prevalences of serum creatinine levels greater than the upper limit of normal (men, 1.2 mg/dL; women, 0.9 mg/dL) in communities at sea level and communities at 500 meters above sea level or higher by sex and age.

MeN
Clinical Presentation of CKD

• Patients usually present with:
  – Asymptomatic yet progressive reduction in eGFR
  – Normal or mildly elevated BP,
  – Low-grade non-nephrotic proteinuria
  – Often hyperuricemia
  – Often hypokalemia.
Mesoamerican Nephropathy

- Tubulointerstitial inflammation and fibrosis
- Secondary glomerulosclerosis
- Glomerular ischemia
Meso-American Nephropathy

• Clinical Presentation:
  – CKD (most common presentation)
  – AKI
  – ESRD
Tropical Medicine Mystery:

What is Killing Young Workers in Central America?
Possible infectious etiologies

- Leptospirosis
- Hantavirus
- Malaria
- Dengue (rare: ARF due to rhabdomyolysis)
- Cytomegalovirus
- *Mansonella ozzardi/perstans* (common in sugar cane workers)
- Hepatitis B (membranous nephropathy, mesangiocapillary glomerulonephritis); Hepatitis C (cryoglobulinemia-mediated glomerulonephritis); Hepatitis E (acute tubular necrosis)
- *Streptococcus*
- *Leishmania*
- HIV
Hypothesis:
An infectious agent, possibly a zoonotic pathogen could be transmitted through water/soil in field, vectors, or contact with animals. Reservoir hosts may play an important role in maintaining the epidemic.
Findings in 93 patients with MAN

- Antibodies to Leptospira and Hantavirus: 10%
- Antibodies to Leptospira: 40%
- Antibodies to Hantavirus: 9%
- NO Antibodies to Leptospira or Hantavirus: 41%
Concomitant Medications

- Acetaminofin/Paracetamol: 79.43%
- Ibuprofen: 26.95%
- Diclofenac: 9.93%
- Naproxeno: 0.71%
- Metamizol: 0.00%

Tipo de NSAID: Acetaminofin/Paracetamol
Proposed mechanism for Mesoamerican nephropathy

Exercise, heat, and recurrent dehydration

- Low grade muscle injury
  - ↑Uric acid load
    - Hyperuricemia
      - Glomerular effects

- Volume (salt) loss
  - ↓Urine pH with crystalluria

- Dehydration (water) loss
  - ↑Serum osmolarity
    - Vasopressin
      - Aldose reductase
      - Fructokinase
    - Rehydration with sugary beverages

↑Uric acid concentration

Repeated acute kidney injury
  - Chronic kidney disease

Meso-American Nephropathy (MeN): Is the Problem Dehydration or Rehydration?
MESOAMERICAN NEPHROPATHY

REHYDRATION with Contaminated H₂O

DEHYDRATION

Reduced Renal Perfusion

Concentrated Renal Medulla

Accumulation of toxins in Renal Tubules

RENAL INJURY

Campese V, NDT 2016
Are the lesions seen in MaN linked to Calcineurin Inhibition?

- EM shows big and dysmorphic lysosomes with light medium uniform electron dense matrix containing disperse dark electron dense deposits
- Cyclosporin LM causes similar lysosomal injury
- Aristolochic acid does not cause this type of lesions.
- Is this autophagy? Like seen with cyclosporin A?
- In Country that produce wine and use pesticides they have CINAC
- There is certainly in Europe a relationship between development of that lesion and use of pesticides
- In rats, dehydration did not cause these lesions, but when dehydration was accompanied with cyclosporine then the lysosomes lesions would appear

De Brod 2018
increased size and number of dysmorphic lysosomes with light-medium uniform electron-dense matrix containing dispersed dark electron-dense non-membrane bound “aggregates”.

Kidn Intern in rev oct 2018
B Vervaet, M De Broe et al
Chronic Interstitial Nephritis in Agricultural Communities (CINAC) 1995-2018

Red: countries were these typical proximal tubular lesions were indentified in renal biopsies odf patiets with CINAC
Yellow under investigation, in India we have very recently also found these lesions

• All insecticidal Type II pyrethroids (cypermethrin, deltamethrin and fenvalerate) are potent inhibitors of isolated calcineurin from bovine brain.

• Herbicides, such as Paraquat, stimulate \( \text{H}_2\text{O}_2 \) production. This, in turn, inhibit calcineurin phosphatase activity and can cause AKI as well as CKD.

• Lomustine and Clomiphene (chemotherapeutics) are calcineurin type inhibitors and cause the same lesions
Summary and Conclusions

• The symbiosis between human and environment has become precarious.
• A growing number of diseases are caused by environmental factors.
• The kidney is particularly susceptible to environmental insults.
• An epidemic of CKD of enormous proportion is affecting several regions in Central America, Asia and Africa.
• The disease affects primarily young workers subjected to strenuous heat and working conditions.
• The disease can progress rapidly.
• The cause(s) remain unknown but environmental toxins in conjunction with dehydration appear to be critical factors.